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<b>(54) Title:</b> COMPOSITIONS FOR THE TREATMENT OF DERMATOLOGICAL DISORDERS AND METHODS FOR THEIR USE		
<b>(57) Abstract</b>  The present invention provides compositions and methods for alleviation of both visible and non-visible, or pre-emergent, dermatological lesions associated with changes in normal keratinization, cutaneous infection, epidermal formation or pilosebaceous function, such as acne, psoriasis, seborrhea, ingrown hairs and pseudofolliculitis barbae, and hyperpigmented skin. The inventive compositions comprise a dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent; a dermatologically absorbable alpha or beta hydroxy acid; and a dermatologically absorbable zinc compound in a suitable carrier.		

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**COMPOSITIONS FOR THE TREATMENT  
OF DERMATOLOGICAL DISORDERS  
AND METHODS FOR THEIR USE**

5

**Technical Field of the Invention**

This invention relates to compositions for the treatment of dermatological disorders and, in particular, to topical compositions for the treatment of dermatological conditions arising from changes in normal keratinization, epidermal formation or pilosebaceous function, such as acne, psoriasis, seborrhea, ingrown hairs and pseudofolliculitis barbae, and hyperpigmented skin.

10

**Background of the Invention**

Acne, cutaneous infections, psoriasis and other disorders of the cutaneous and pilosebaceous unit or the process of keratogenesis are typically characterized by the presence of visible dermatological lesions, such as the raised closed comedones, the often colored open comedones, red or pustular-looking inflamed papules, pustules, nodules and cysts of acne or cutaneous infection; the readily visible ingrown hairs of pseudofolliculitis barbae; or the visible scales of seborrhea, ichthyosis and psoriasis. Clinical evaluation of potential treatments for such disorders is typically based on the effectiveness of the treatment in reducing the number and severity of these visible lesions.

15

20

Prior to the eruption of visible lesions on the surface of the skin, non-visible lesions, herein referred to as pre-emergent lesions, are generally present within the skin. While pre-emergent lesions are insufficiently visible to be graded in conventional clinical studies, their presence within the skin can be discerned by the tactile sense of feel and/or by pain and tension within the skin.

25

Pre-emergent lesions are caused by a pre-emergent process within the epidermis and dermis, or within and surrounding the pilosebaceous follicle, which is located within the skin's epidermis, dermis, or both. In acne, for example, this pre-emergent process usually begins within the pilosebaceous follicle. The pilosebaceous follicle is filled with sebum secreted into the follicle by the sebaceous gland, bacteria, (primarily corynebacterium acnes, or P. acnes) and keratin cells

30

which slough off the inner wall of the follicle. In the pre-emergent process, the follicular wall is attacked by inflammatory agents, in particular excess free fatty acids produced by the breakdown of triglycerides present in the sebum by lipolytic enzymes, or lipases, and chemotactic and inflammatory agents that are produced and induced from P. acnes. Research has shown that, compared to normal patients, acne patients have increased levels of sebum secretion and increased presence of P. acnes and its associated lipase activity, with a resulting increase in the level of free fatty acids and other associated inflammatory agents. These increases have been shown to be roughly proportional to the severity of the disorder.

In addition, acne patients often have abnormal follicular walls. In normal skin, the follicular wall is composed entirely of keratinized cells, formed by the process of keratinization. This keratinized cell wall forms a barrier between the sloughed keratin cells, and the sebaceous and bacterial components within the follicle and the aqueous tissue surrounding the follicle. In acne patients, faulty keratinization apparently allows structurally weaker sebum-containing cells to be inserted into the follicular wall, thereby making the wall more vulnerable to attack and rupture. Once the cell wall is breached, free fatty acids, sebaceous and inflammatory components, live and dead bacteria, sloughed cells from the follicular wall and other follicle contents are released into the aqueous tissue surrounding the follicle, where they establish an inflammatory process (Webster, G., Jnl. Am. Acad. Dermatol., 1955; 33:247-253).

The pre-emergent process described above can progress to the point where, though not visible on the surface, the inflammation and resulting internal lesions can be felt within the skin as a sensation or as pain, and may also be felt by touch on the surface of the skin as a bump.

While several studies have been published on the individual effects of agents such as benzoyl peroxide, alpha hydroxy acids and zinc agents on dermatological problems visible on the surface of the skin, such as non-inflamed comedones, inflamed papules and pustules, cutaneous infections, ingrown hairs, and keratotic scales (Handbook of Non-Prescription Drugs, American Pharmaceutical Association, 9th Ed. (1990) 798; Goodman and Gilman, Pharmacologic Basis of

Therapeutics, MacMillan Publishing Co., 6th Ed. (1980), 977; Ruey, J.Y., Van Scott, E.J., U.S. Patent No. 4,363,815), the inventors are unaware of any published reports of the efficacy of recognized acne drugs on pre-emergent lesions.

5     **Summary of the Invention**

          The present invention provides a method of treating dermatological disorders arising from changes in normal keratinization, epidermal formation or pilosebaceous function, such as acne, psoriasis, seborrhea, ingrown hairs and pseudofolliculitis barbae, and hyperpigmented skin, by the topical administration of  
10     a composition comprising a dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent; a dermatologically absorbable alpha or beta hydroxy acid; and a dermatologically absorbable zinc compound in a dermatologically acceptable carrier. The compositions of the present invention are preferably applied to an affected area of a patient's skin on a daily basis, in the  
15     form of clear gels, opaque gels, lotions, suspensions, ointments, creams, powders and the like.

          The dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent is preferably selected from the group consisting of azoleic acid, benzoyl peroxide, erythromycin, bacitracin, zinc bacitracin,  
20     polymyxin, neomycin, chloramphenicol, tetracycline, minocycline, clindamycin, doxycycline, undecylenic acid and salts thereof, propionic acid and salts thereof, caprylic acid and salts thereof, ciprofloxacin, cephalosporins, benzoic acid, ciclopirox olamine, clotrimazole, econazole nitrate, metronidazole, miconazol nitrate, ketoconazole, oxiconazole, tolnaftate and combinations thereof; and is most  
25     preferably benzoyl peroxide. The antimicrobial, antibiotic, antibacterial or antifungal agent can be present in an amount of between about 0.1% to about 30%, but may also be used in an amount of between 0.25% to 20%, preferably between about 0.5% to about 10%. All percentages referred to herein are by weight.

          The alpha or beta hydroxy acid agent is selected from the group  
30     consisting of free acids, salts, amides, amphoteric and polymeric forms of the following compounds: citric acid, glycolic acid, glucuronic acid, galacturonic acid,

glucuronolactone, gluconolactone, alpha-hydroxybutyric acid, alpha-hydroxyisobutyric acid, lactic acid, malic acid, mandelic acid, mucic acid, pyruvic acid, methyl pyruvate, ethyl pyruvate, beta-phenyllactic acid, beta-phenylpyruvic acid, quinnic acid, saccharic acid, tartaric acid, tartronic acid and beta-

5 hydroxybutyric acid. In a preferred embodiment, the alpha or beta hydroxy acid is selected from the group consisting of glycolic acid, lactic acid, mandelic acid, citric acid, tartaric acid, malic acid, salicylic acid, and acetylsalicylic acid, and is most preferably glycolic acid or lactic acid. The alpha or beta hydroxy acid is present in an amount of between about 0.10% to about 70%, with a preferred concentration

10 for brief application on the skin of between about 5% to about 70%, with a preferred concentration for daily use left on the skin after application of between about 0.15% to about 15%.

The zinc compound is selected from the group consisting of water soluble, poorly water soluble and water insoluble zinc salts, compounds and

15 complexes, such as zinc acetate, zinc bacitracin, zinc bromide, zinc cysteate, zinc caprylate, zinc chloride, zinc citrate, zinc fluoride, zinc formate, zinc glycinate, zinc iodate, zinc lactate, zinc nitrate, zinc nitrite, zinc oleate, zinc oxalate, zinc oxide, zinc permanganate, zinc peroxide, zinc phenolsulfonate, zinc phosphate, zinc propionate, zinc pyrophosphate, zinc ricinoleate, zinc salicylate, zinc selenate, zinc

20 silicate, zinc selenide, zinc sulfate, zinc stearate, zinc sulfide, zinc tannate, zinc tartrate, zinc valerate, zinc peptides, and zinc protein complexes. In a preferred embodiment of the present invention, the zinc compound is zinc lactate or zinc acetate, and is present in an amount of between about 0.001% to about 30%, most preferably between about 0.1% to about 10%.

25 Other therapeutic agents may be usefully added to the compositions of the present invention. Such agents include retinoids, such as trans retinoic acid, 13-cis retinoic acid and derivatives thereof; anti-androgens, such as spironolactone; metronidazole; and anti-inflammatory agents, such as hydrocortisone, betamethasone, clobetasole, fluocinonide, triamcinolone, desonide, and halcinonide.

30 These therapeutic agents may be present in an amount of between about 0.001% to about 10.0%, preferably between about 0.01% to 5.0%.

The active ingredients of the present invention are combined in a dermatologically acceptable carrier composed of noncomedogenic and hypoallergenic agents, such as water, C<sub>12-15</sub> alkyl benzoate, glycerin, cetyl stearyl alcohol, polyacrylamide, C<sub>13-14</sub> isoparaffin, laureth-7, PEG-1000 stearate, steareth S-2, steareth S-20, sodium hydroxide, dimethicone, and disodium EDTA. Special Petrolatum Fraction, a more viscous form of Petrolatum U.S.P., having a higher proportion of longer chain molecules is especially useful. Other carriers which may be usefully employed in the present invention are well known in the art.

## 10 Detailed Description of the Invention

### Example 1

Two formulations of the inventive composition, Formulas I and II, composed of the reagents shown in Table I were prepared using the following protocol.

15 Dissolve the disodium EDTA and the zinc lactate in 60°C hot water (30% batch weight) and add the glycerin. Then add the polyacrylamide-C<sub>13-14</sub> Isoparaffin-Laureth-7, and mix until uniform, to provide part A. Separately, dissolve the glycolic acid in an equal part of water and slowly add the sodium hydroxide. Add to part A and maintain at 60°C. Separately, heat steareth S-2 and  
20 S-20, glycerylmonostearate SE and cetylstearyl alcohol until fluid and uniform. Add this to part A with mixing until smooth. Add the dimethicone; start cooling to 40°C. Separately, disperse the benzoyl peroxide in the C<sub>12-15</sub> alkyl benzoate and add to cooled part A. Finally, QS with water to 100% and homogenize if  
25 necessary.

TABLE I

		<u>% BY WEIGHT</u>	
		FORMULA I	FORMULA II
5	benzoyl peroxide	10.0	6.0
	C12-15 benzoate ester	7.0	7.0
	glycerin	6.0	6.0
	cetyl stearyl alcohol (C5-50, LIPO)	4.0	4.0
	polyacrylamide, C12-14 isoparaffin and laureth-7	3.0	3.0
10	glycolic acid	4.0	2.0
	sodium hydroxide	0.5	0.5
	steareth S-2 (LIPO)	2.0	2.0
	glycerylmonostearate, SE	2.0	2.0
15	steareth S-20 (LIPO)	1.5	1.5
	dimethicone 200 fluid (100 cps) (Dow Corning)	1.0	1.0
	zinc lactate	0.6	0.6
	disodium EDTA	0.5	0.5
20	strontium chloride	2.5	2.5
	water	to 100%	to 100%

A third formulation of the inventive composition, specifically a gel that can be used as a cleanser or left on the skin for treatment, hereinafter referred to as Formula III, composed of the reagents shown in Table II was prepared as follows.

Petrolatum, sodium cocyl isethionate, potassium metaphosphate, titanium dioxide and zinc lactate were mixed and homogenized until smooth to form mixture I. Carbomer was dispersed in a portion of the glycerin, heated to 75°C and



added to mixture I, homogenizing if necessary until creamy, to form mixture II. Glycolic acid was dissolved in the remaining glycerin at 50°C. To this was added sodium hydroxide, previously dissolved in 5 parts of water. The resulting mixture was added to mixture II and then cooled to 45°C to provide mixture III. Benzoyl peroxide was dispersed in C12-15 alkyl benzoate and added to mixture III. The resulting product was milled as needed.

TABLE II

		<u>% BY WEIGHT</u>
10	glycerin, anhydrous	50.0
	petrolatum	15.0
	benzoyl peroxide	10.0
	zinc lactate	2.0
	sodium cocyl isethionate	4.0
15	alfa olefin sulfonate	2.0
	potassium metaphosphate	0.5
	C12-15 alkyl benzoate	5.0
	glycolic acid	0.25
	sodium hydroxide	0.05
20	carbomer	0.7
	water	to 100%

Example 2

Formula III of Example 1 was tested on two patients having persistent dermatological lesions; the lesions of both occurring mostly on the face and on the neck.

Both patients had suffered continually from inflamed papules, non-inflamed ingrown hairs, inflamed ingrown hairs and pre-emergent lesions. Prior to treatment with Formula III of the present invention, each patient had used a wide range of treatments, including topical benzoyl peroxide, topical erythromycin, topical erythromycin plus zinc, topical clindamycin, alpha hydroxy acid lotions, and

topical erythromycin plus topical benzoyl peroxide. Each of these medications was used individually on a daily basis for at least two months. Each medication initially caused a reduction in the number and severity of dermatological lesions but this effect subsequently diminished. None of the medications was successful in substantially and consistently reducing the lesions, particularly the pre-emergent lesions.

Prior to treatment with Formula III of the present invention, the patients had a range of dermatological problems as shown in Table III.

10

TABLE III

	<u>Patient 1</u>	<u>Patient 2</u>
Emerging lesions	3 to 6	4 to 8
Redness	moderate patches	mild-moderate
15 Papules	1 to 2	2 to 4
Ingrown hairs	1 to 3	2 to 5

Each patient applied Formula III topically twice daily to the effected area. The range of dermatological lesions present after treatment for one month and two months are shown in Tables IV and V, respectively.

20

TABLE IV

	<u>Patient 1</u>	<u>Patient 2</u>
25 Emerging lesions	1 to 2	0 to 3
Redness	mild-none	none
Papules	0 to 1	0 to 2
Ingrown hairs	0 to 2	1 to 2

30

TABLE V

	<u>Patient 1</u>	<u>Patient 2</u>
Emerging lesions	0 to 1	0 to 2
Redness	none	none
5 Papules	0	0
Ingrown hairs	0 to 1	0

10        These results demonstrate that the compositions of the present invention are effective in reducing the number and severity of both visible lesions, such as papules, and non-visible, pre-emergent lesions.

         Although the present invention has been described in terms of specific embodiments, changes and modifications can be carried out without departing from the scope of the invention which is intended to be limited only by the scope of the appended claims.

**Claims**

1. A composition for the treatment of dermatological disorders associated with changes in normal keratinization, epidermal formation or pilosebaceous function, comprising:

- 5 (a) a dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent;
- (b) a dermatologically absorbable alpha or beta hydroxy acid; and
- (c) a dermatologically absorbable zinc compound in a dermatologically acceptable carrier.

10 2. The composition of claim 1, wherein the dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent is selected from the group consisting of: azoleic acid, benzoyl peroxide, erythromycin, bacitracin, zinc bacitracin, polymyxin, neomycin, chloramphenicol,

15 tetracycline, minocycline, clindamycin, doxycycline, undecylenic acid and salts thereof, propionic acid and salts thereof, caprylic acid and salts thereof, ciprofloxacin, cephalosporins, benzoic acid, ciclopirox olamine, clotrimazole, econazole nitrate, metronidazole, miconazol nitrate, ketaconazole, oxiconazole, tolnaftate and combinations thereof.

20 3. The composition of claim 1, wherein the dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent is benzoyl peroxide.

25 4. The composition of claim 1, wherein the dermatologically absorbable alpha or beta hydroxy acid is selected from the group consisting of: citric acid, glycolic acid, glucuronic acid, galacturonic acid, glucuronolactone, gluconolactone, alpha-hydroxybutyric acid, alpha-hydroxyisobutyric acid, lactic acid, malic acid, mandelic acid, mucic acid, pyruvic acid, methyl pyruvate, ethyl

30 pyruvate, beta-phenyllactic acid, beta-phenylpyruvic acid, quinnic acid, saccharic

acid, tartaric acid, tartronic acid and beta-hydroxybutyric acid, and salts, amides, amphoteric and polymeric forms thereof.

5           5.     The composition of claim 4, wherein the dermatologically absorbable alpha or beta hydroxy acid is selected from the group consisting of: glycolic acid, salicylic acid, and lactic acid.

10           6.     The composition of claim 1, wherein the dermatologically absorbable zinc compound is selected from the group consisting of: zinc acetate, zinc bacitracin, zinc bromide, zinc cysteate, zinc caprylate, zinc chloride, zinc citrate, zinc fluoride, zinc formate, zinc glycinate, zinc iodate, zinc lactate, zinc nitrate, zinc nitrite, zinc oleate, zinc oxalate, zinc oxide, zinc permanganate, zinc peroxide, zinc phenolsulfonate, zinc phosphate, zinc propionate, zinc pyrophosphate, zinc ricinoleate, zinc salicylate, zinc selenate, zinc silicate, zinc selenide, zinc sulfate, zinc stearate, zinc sulfide, zinc tannate, zinc tartrate, zinc valerate, zinc peptides, and zinc protein complexes.

20           7.     The composition of claim 1, wherein the dermatologically absorbable zinc compound is selected from the group consisting of: zinc lactate and zinc acetate.

25           8.     The composition of claim 1, wherein the dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent is present in an amount of between about 0.25% to 20%.

          9.     The composition of claim 1, wherein the dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent is present in an amount of between about 0.5% to about 10%.

10. The composition of claim 1, wherein the dermatologically absorbable alpha or beta hydroxy acid is present in an amount of between about 0.15% to 15%.

5 11. The composition of claim 1, wherein the dermatologically absorbable alpha or beta hydroxy acid is present in an amount of between about 0.5% to about 15%.

10 12. The composition of claim 1, wherein the dermatologically absorbable zinc compound is present in an amount of between about 0.1% to about 10%.

13. The composition of claim 1, wherein:  
(a) the dermatologically absorbable topical antimicrobial, antibiotic,  
15 antibacterial or antifungal agent is benzoyl peroxide;  
(b) the dermatologically absorbable alpha or beta hydroxy acid is selected from the group consisting of glycolic acid, salicylic acid, and lactic acid; and  
(c) the dermatologically absorbable zinc compound is selected from the  
20 group consisting of zinc lactate and zinc acetate.

14. The composition of claim 1, additionally comprising a therapeutic agent selected from the group consisting of: retinoids and anti-inflammatory agents and anti-androgens.

25 15. A composition for the treatment of pre-emergent, dermatological lesions associated with changes in normal keratinization, epidermal formation or pilosebaceous function, or infection, comprising:

(a) a dermatologically absorbable topical antimicrobial, antibiotic,  
30 antibacterial or antifungal agent;  
(b) a dermatologically absorbable alpha or beta hydroxy acid; and

(c) a dermatologically absorbable zinc compound in a dermatologically acceptable carrier.

16. The composition of claim 13, wherein:

5 (a) the dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent is benzoyl peroxide;

(b) the dermatologically absorbable alpha or beta hydroxy acid is selected from the group consisting of glycolic acid, salicylic acid, and lactic acid; and

10 (c) the dermatologically absorbable zinc compound is selected from the group consisting of zinc lactate and zinc acetate.

17. A method for the treatment of dermatological disorders associated with changes in normal keratinization, epidermal formation or pilosebaceous function, or infection comprising administering a composition comprising:

15 (a) a dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent;

(b) a dermatologically absorbable alpha or beta hydroxy acid; and

20 (c) a dermatologically absorbable zinc compound in a dermatologically acceptable carrier.

18. The method of claim 15, wherein the dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent is selected from the group consisting of: azoleic acid, benzoyl peroxide, erythromycin, bacitracin, zinc bacitracin, polymyxin, neomycin, chloramphenicol, tetracycline, minocycline, clindamycin, doxycycline, undecylenic acid and salts thereof, propionic acid and salts thereof, caprylic acid and salts thereof, ciprofloxacin, cephalosporins, benzoic acid, ciclopirox olamine, clotrimazole, econazole nitrate, metronidazole, miconazol nitrate, ketoconazole, oxiconazole, tolnaftate and combinations thereof.

30

19. The method of claim 16, wherein the dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent is benzoyl peroxide.

5           20. The method of claim 15, wherein the dermatologically absorbable alpha or beta hydroxy acid is selected from the group consisting of: citric acid, glycolic acid, glucuronic acid, galacturonic acid, glucuronolactone, gluconolactone, alpha-hydroxybutyric acid, alpha-hydroxyisobutyric acid, lactic acid, malic acid, mandelic acid, mucic acid, pyruvic acid, methyl pyruvate, ethyl pyruvate, beta-  
10 phenyllactic acid, beta-phenylpyruvic acid, quinnic acid, saccharic acid, tartaric acid, tartronic acid and beta-hydroxybutyric acid, and salts, amides, amphoteric and polymeric forms thereof.

21. The method of claim 18, wherein the dermatologically absorbable  
15 alpha or beta hydroxy acid is selected from the group consisting of: glycolic acid, salicylic acid, and lactic acid.

22. The method of claim 15, wherein the dermatologically absorbable zinc compound is selected from the group consisting of: zinc acetate, zinc  
20 bacitracin, zinc bromide, zinc cysteate, zinc caprylate, zinc chloride, zinc citrate, zinc fluoride, zinc formate, zinc glycinate, zinc iodate, zinc lactate, zinc nitrate, zinc nitrite, zinc oleate, zinc oxalate, zinc oxide, zinc permanganate, zinc peroxide, zinc phenolsulfonate, zinc phosphate, zinc propionate, zinc pyrophosphate, zinc ricinoleate, zinc salicylate, zinc selenate, zinc silicate, zinc selenide, zinc sulfate,  
25 zinc stearate, zinc sulfide, zinc tannate, zinc tartrate, zinc valerate, zinc peptides, and zinc protein complexes.

23. The method of claim 20, wherein the dermatologically absorbable zinc compound is selected from the group consisting of: zinc lactate and zinc  
30 acetate.



24. The method of claim 15, wherein the dermatological disorder is selected from the group consisting of acne, psoriasis, seborrhea, ingrown hairs, pseudofolliculitis barbae, hyperpigmented skin, and cutaneous infection.

5           25. A method for the treatment of pre-emergent lesions associated with changes in normal keratinization, epidermal formation or pilosebaceous function, comprising administering a composition comprising:

- (a) a dermatologically absorbable topical antimicrobial, antibiotic, antibacterial or antifungal agent;
- 10           (b) a dermatologically absorbable alpha or beta hydroxy acid; and
- (c) a dermatologically absorbable zinc compound in a dermatologically acceptable carrier.

26. The method of claim 23, wherein the dermatologically absorbable  
15           topical antimicrobial, antibiotic, antibacterial or antifungal agent is selected from the group consisting of: azoleic acid, benzoyl peroxide, erythromycin, bacitracin, zinc bacitracin, polymyxin, neomycin, chloramphenicol, tetracycline, minocycline, clindamycin, doxycycline, undecylenic acid and salts thereof, propionic acid and salts thereof, caprylic acid and salts thereof, ciprofloxacin, cephalosporins, benzoic  
20           acid, ciclopirox olamine, clotrimazole, econazole nitrate, metronidazole, miconazole nitrate, ketoconazole, oxiconazole, tolnaftate and combinations thereof.

27. The method of claim 24, wherein the dermatologically absorbable  
25           topical antimicrobial, antibiotic, antibacterial or antifungal agent is benzoyl peroxide.

28. The method of claim 23, wherein the dermatologically absorbable  
alpha or beta hydroxy acid is selected from the group consisting of: citric acid, glycolic acid, glucuronic acid, galacturonic acid, glucuronolactone, gluconolactone,  
30           alpha-hydroxybutyric acid, alpha-hydroxyisobutyric acid, lactic acid, malic acid, mandelic acid, mucic acid, pyruvic acid, methyl pyruvate, ethyl pyruvate, beta-

phenyllactic acid, beta-phenylpyruvic acid, quinnic acid, saccharic acid, tartaric acid, tartronic acid and beta-hydroxybutyric acid, and salts, amides, amphoteric and polymeric forms thereof.

5           29.    The method of claim 26, wherein the dermatologically absorbable alpha or beta hydroxy acid is selected from the group consisting of: glycolic acid, salicylic acid, and lactic acid.

10           30.    The method of claim 23, wherein the dermatologically absorbable zinc compound is selected from the group consisting of: zinc acetate, zinc bacitracin, zinc bromide, zinc cysteate, zinc caprylate, zinc chloride, zinc citrate, zinc fluoride, zinc formate, zinc glycinate, zinc iodate, zinc lactate, zinc nitrate, zinc nitrite, zinc oleate, zinc oxalate, zinc oxide, zinc permanganate, zinc peroxide, zinc phenolsulfonate, zinc phosphate, zinc propionate, zinc pyrophosphate, zinc  
15   ricinoleate, zinc salicylate, zinc selenate, zinc silicate, zinc selenide, zinc sulfate, zinc stearate, zinc sulfide, zinc tannate, zinc tartrate, zinc valerate, zinc peptides, and zinc protein complexes.

20           31.    The method of claim 28, wherein the dermatologically absorbable zinc compound is selected from the group consisting of: zinc lactate and zinc acetate.

          32.    The method of claim 23, wherein:  
          (a)    the dermatologically absorbable topical antimicrobial, antibiotic,  
25   antibacterial or antifungal agent is benzoyl peroxide;  
          (b)    the dermatologically absorbable alpha or beta hydroxy acid is selected from the group consisting of glycolic acid, salicylic acid, and lactic acid;  
          and  
          (c)    the dermatologically absorbable zinc compound is selected from the  
30   group consisting of zinc lactate and zinc acetate.

33. The method of claim 23, wherein the dermatological disorder is selected from the group consisting of acne, psoriasis, seborrhea, ingrown hairs, pseudofolliculitis barbae, hyperpigmented skin, and cutaneous infection.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/14617

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6    A61K7/48    A61K33/30    A61K31/00    A61K31/60    A61K31/19		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6    A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 380 157 A (EVERS MATTHIJS CORNELIS) 1 August 1990  see page 2, line 24-55 see page 3, line 5-15; claims 1,3-5,7,8,10 ---	1-6, 8-11,15, 17-22, 25-30  13,16,32
A	---	
X	EP 0 281 812 A (MILOR SCIENT LTD) 14 September 1988  see column 6, line 35-42; example 1 see column 5, line 14-28 see column 4, line 19-22; claims 1-7,11-20 --- -/--	1,2, 4-12,14, 15,17, 18, 20-26, 28-31,33
<div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</span> <span><input checked="" type="checkbox"/> Patent family members are listed in annex.</span> </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents:</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center; font-weight: bold;">17 February 1997</div>		Date of mailing of the international search report  <div style="text-align: center; font-weight: bold;">28.02.97</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016		Authorized officer  <div style="text-align: center; font-weight: bold;">Kanbier, D</div>

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/14617

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 37 04 214 A (WACHTL HAIDE DR MED) 25 August 1988  see the whole document ---	1,2,4-6, 8-11,15, 17,18, 20-22, 24-26, 28-30,33
X	DATABASE WPI Week 9504 Derwent Publications Ltd., London, GB; AN 95-024628 XP002025455 & ES 2 061 407 (CASTILLA CID C.A.) , 1 December 1994 see abstract & ES 2 061 407 A (CASTILLA CID C.A.) 1 December 1994 see the whole document ---	1,2,4-6, 8-12,15, 17,18, 20-22, 24-26, 28-30,33
X	EP 0 661 036 A (OREAL) 5 July 1995  see page 6, line 15-30; claims 1,12,13,16,17 ---	1,2,4-6, 14,15, 17,18, 20-22, 24-26, 28-30,33
X	EP 0 413 528 A (YU R.J.) 20 February 1991  see page 3, line 16-30; examples 47,48,50 see page 3, line 42-55 see page 5, line 15 - page 6, line 54 see page 7, line 16-58 see page 10, line 6-23 see page 27, line 6-30; claims 1,3-6,8-10,12,13,18-20 ---	1-6, 13-22, 24-30, 32,33
X	EP 0 086 070 A (UNILEVER NV) 17 August 1983  see page 13, paragraph 2 ---	1,2,4-6, 15,17, 18, 20-22, 24-26, 28-30,33

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/14617

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 23587 A (PROCTER & GAMBLE) 8 September 1995  see page 10, line 2-25; claims 2,7; example 2 ---	1-5, 8-11, 13-21, 24-29, 32,33
A	US 4 514 385 A (DAMANI NALINKANT C ET AL) 30 April 1985  see column 2, line 51-64; claim 1; examples 1,2 -----	1-5, 8-11,13, 15-21, 24-29, 32,33

# INTERNATIONAL SEARCH REPORT

national application No.

PCT/US 96/ 14617

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 17-33  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
  
See next page
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 14617

FURTHER INFORMATION CONTINUED FROM PCT/SA/210

i. A compound cannot be sufficiently characterized by its pharmacological profile or its mechanism of action as it is done in Claims 1, 8, 9, 14, 15, 17 and 25 as:  
"antimicrobial, antibiotic, antibacterial or antifungal agent", "anti-inflammatroy agents"; "anti-androgens".

The search has been executed based on compounds specifically mentioned in Claims 2-7, 13, 16, 18-23 and 26-32 and in Example 1.

ii. In view of the large number of compounds, which are defined by the general formula used in Claims 1(b), 10, 11, 14, 15(b), 17(b) and 25(b), the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data were given and the specific compounds mentioned in Claims 2-7, 13, 16, 18-23 and 26-32 and in Example 1, and to the general idea underlying the application (see Guidelines, part B, chapter III, paragraph 3.6).



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/14617

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/14617

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		JP-A- 58134009	10-08-83
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